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| 09/419,817 | 10/13/99 | HUANG X | 03848.80923 |

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| EXAMINER | |
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| FORMAN, B | |
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**DATE MAILED:** 09/11/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/419,817 | Applicant(s) HUANG ET AL. | |
|---|---|---|---|
| | Examiner BJ Forman | Art Unit 1655 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16 and 23-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12 13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

1. This action is in response to papers filed 26 June 2001 in Paper No. 12 in which Applicant requested reconsideration of the previous rejections in the Office Action of Paper No. 11 dated 26 March 2001. The previous rejections are withdrawn in view of the arguments and new grounds for rejection. All of the arguments have been thoroughly reviewed but are deemed moot in view of the withdrawn rejections and new grounds for rejection. New grounds for rejection are discussed.

Currently claims 1-16 and 23-38 are under prosecution.

***Information Disclosure Statement***

2. The copy of the information disclosure statement filed 7 February 2000 is acknowledged and has been entered into the application. The references have been considered, the 1449 has been initialed and a copy of the initialed 1449 is enclosed.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 4, 5, 7, 8, 9, 11-14, 16, 23, 24, 26, 27, 29, 30, 31, 33-36 & 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Lane et al. (U.S. Patent No. 6,165,714, filed 16 December 1997).

Regarding Claims 1 & 23, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample (Column 2, lines 31-38), the method comprising amplifying a region of DNA comprising the polymorphic locus (Example 3, Column 12, lines 19-30 and primers PM and MM), wherein the primer comprises a 3' portion which is complementary to the region of DNA (Column 7, lines 23-26 and Fig. 3A) and a 5' portion which is complementary to all or part of a probe on a solid support and not complementary to the region of DNA (Column 7, lines 43-49), labeling the amplified DNA to form labeled amplified DNA products (Column 3, lines 54-60) and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56). Vary et al. do not teach the comprising a primer pair wherein the first primer comprises a 5' portion which is identical in sequence to all of a probe on a solid support. Lane et al. teach a similar method to determine a nucleotide analyte comprising: amplifying a region of DNA comprising using a primer pair, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe; hybridizing the amplified products to the probe on the support such that the second strand hybridizes to the support; and detecting the amplified products wherein the presence of amplified products indicates the nucleic acid sample contains the nucleotide analyte (Column 8, lines 36-41 and 9B). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' portion of the primer being complementary to the capture-probe in the method of Vary et al. with the 5' portion being identical to the capture probe as taught by Lane et al. to thereby immobilize the sense strand for the expected benefit detecting the presence of

a polymorphism in the coding strand. Additionally, one skilled in the art would have been motivated to modify the single primer amplification of Vary et al. with primer pair amplification of Lane et al. to thereby synthesize the second strand for the obvious benefit of providing the second strand itself or in addition to the first strand to thereby more accurately determine the presence of the polymorphic locus by analyzing the presence and quantity of both the first and second strands.

Regarding Claims 2 & 24, Vary et al. teach the method wherein the labeling couples a labeled nucleotide to a 3' end (Column 3, lines 54-61).

Regarding Claims 4 & 26, Vary et al. teach the method wherein the nucleotide is labeled (Column 3, lines 54-61) but they do not teach the nucleotide is fluorescently labeled. Lane et al. teach the similar method wherein the nucleotide is fluorescently labeled thereby providing detection and distinction of multiple targets (Column 12, line 61-Column 13, line 4). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the label of Vary et al. with the fluorescent label of Lane et al. for the expected benefits of increased flexibility and cost effectiveness of the method as taught by Lane et al. (Column 13, lines 1-4).

Regarding Claims 5 & 27, Vary et al. teach the method wherein the nucleotide is radioactively labeled with $^{32}$P-dATP (Column 3, lines 54-59).

Regarding Claims 7 & 29, Vary et al. teach the method wherein the nucleotide is epitopically labeled wherein the epitope is a halogen-modified nucleotide which is antibody-detected (Column 3, lines 63-65 and Column 4, line 66-Column 5, line2).

Regarding Claims 8 & 30, Vary et al. teach the method further comprising detecting the label on the solid support (Column 4, lines 53-56). Lane et al. teach the similar method wherin the fluorescent label is detected optically on the solid support i.e. by differing color (Column 12, lines 61-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the radioactive label of Vary et al. with the fluorescently

labeled nucleotide and optical detection of Lane et al. for the obvious benefits of eliminating the radioactive labels i.e. reduced hazard exposure and for the expected benefit of providing distinguishable signals which increase the flexibility and cost effectiveness of the assays as taught by Lane et al. (Column 13, lines 1-4).

Regarding Claims 9 & 31, Vary et al. do not teach the method wherein two pairs of primers are used. Lane et al. teach the similar method wherein two primer pairs are used i.e. a primer pair for each nucleic acid analyte (Column 12, lines 61-65). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single primer of Vary et al. with the two primer pairs of Lane et al. for the obvious benefit of economy of time and labor derived from multiplex assays and for the expected benefits of simultaneous detection and identifying multiple analyte nucleic acids as taught by Lane et al. (Column 6, lines 37-40).

Regarding Claims 11 & 33, Vary et al. do not teach the method wherein two or more target sequences are detected simultaneously. However, Lane et al. teach the similar method wherein two or more target sequences are detected simultaneously (Column 6, lines 26-40). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the single target detection method of Vary et al. with the detection of two or more targets as taught by Lane et al. (Column 6, lines 26-40) for the known benefit of multiplex analysis i.e. economy of time and labor.

Regarding Claims 12 & 34, Vary et al. does not teach the method wherein the sample comprises DNA from two or more individuals. Lane et al. teach the similar method wherein multiple samples are processed simultaneously (Column 6, lines 26-28) but they do not specifically teach the samples comprise DNA from two or more individuals. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made that the multiples samples of Lane et al. encompasses sample from two or more individuals. Therefore, it would have been obvious to one of ordinary skill in the art at the time

the claimed invention was made to apply the multiplex teaching of Lane et al. to the method of Vary et al. and to analyze a sample comprising DNA from two or more individuals for the obvious benefit of economy of time and labor derived from multiplex assays wherein multiple samples can be detected and distinguished for the expected benefits of increased flexibility and cot-effectiveness as taught by Lane et al. (Column 13, lines 1-4)

Regarding Claims 13 & 35, Vary et al. does not teach the method wherein two or more regions of DNA are amplified in a single reaction. Lane et al. teach the similar method wherein two or more regions of DNA are amplified in a single reaction (Column 6, lines 26-40). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the multiplex teaching of Lane et al. to the method of Vary et al. and to analyze two or more DNA regions in a single reaction, wherein each of the regions comprises a polymorphic locus for the obvious benefit of economy of time and labor derived from multiplex assays and for the expected benefits of simultaneous detection and processing of multiple DNA regions as taught by Lane et al. (Column 6, lines 26-40).

Regarding Claims 14 & 36, Vary et al. teach the method comprising a solid support (Column 4, lines 44-56) but they do not teach the solid support is a bead. However, beads as solid supports were well known in the art at the time the claimed invention was made. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the support of Vary et al. with a bead solid support for the known benefits of beads i.e. increased surface area and which provides for increased probe density which facilitates detection of probe hybridzations.

Regarding Claims 16 & 38, Vary et al. teach the method comprising a solid support (Column 4, lines 44-56) but they do not teach the solid support is a high-density array. Lane et al. teach the similar method wherein the solid support is a high-density array (Column 1, lines 22-30). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify solid support of Vary et al. with the high-density array

of Lane et al. for the known benefits of multiplex analysis on a high-density array i.e. detecting multiple targets simultaneously by simply detecting positions on the array (Lane et al., Column 6, lines 38-40).

5. Claims 3, 10, 25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Lane et al. (U.S. Patent No. 6,165,714, filed 16 December 1997), Hames et al. (Nucleic Acid Hybridization: a practical approach, 1988, pages 35, 36 and 42-44) and Lapidus et al. (U.S. Patent No. 5,670,325, filed 14 August 1996).

Regarding Claims 3 & 25, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56) wherein labeling couples a labeled nucleotide to a 3' end (Column 3, lines 54-61). Lane et al. teach a similar method to determine a nucleotide analyte comprising: amplifying a region of DNA comprising using a primer pair, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe; hybridizing the amplified products to the probe on the support such that the second strand hybridizes to the support; and detecting the amplified products wherein the presence of amplified products indicates the nucleic acid sample contains

the nucleotide analyte (Column 8, lines 36-41 and 9B) but Vary et al. and Lane et al. do not teach a terminal transferase catalyzes the step of labeling. However, it was known in the art that terminal transferase labels a 3' end specifically (see Hames et al. page 35-36). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeling of Lane et al. with the terminal transferase catalyzed labeling taught by Hames et al. for the known benefits of terminal transferase specificity as taught by Hames et al. (page 36, first full paragraph).

Regarding Claims 10 & 32, Vary et al. do not teach the method wherein quantities of fluorescent label at known locations on a solid support are detected. Lane et al. teach the similar method wherein quantities of fluorescent label at known locations on the support are compared to determine the presence of nucleic acid analyte (Column 6, lines 37-41) but they do not teach quantities of fluorescent are compared to determine a ration of nucleotides at a polymorphic locus. However, Lapidus et al. teach the similar method wherein the quantities of fluorescent label are compared to thereby determine a ratio of nucleotides at the polymorphic locus i.e. homozygous or heterozygous (Column 18, lines 3-33). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify radioactive polymorphism detection of Vary et al. and position-specific polymorphism detection of Lane et al. with the fluorescent polymorphism detection of Lapidus et al. wherein fluorescent labeled polymorphism are detected to determine a ratio of polymorphic loci for the obvious benefit of eliminating the radioactive detection of Vary et al. (i.e. decreased hazard) and for the expected benefit of accurately determining heterozygosity as taught by Lapidus et al. (Column 18, lines 3-10).

6. Claims 6 & 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Lane et al. (U.S. Patent No. 6,165,714, filed 16 December 1997) and Mullan (U.S. Patent No. 5,455,169, filed 4 June 1992).

Regarding Claims 6 & 28, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support (Column 4, lines 44-56) to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56). Lane et al. teach a similar method to determine a nucleotide analyte comprising: amplifying a region of DNA comprising using a primer pair, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe; hybridizing the amplified products to the probe on the support such that the second strand hybridizes to the support; and detecting the amplified products wherein the presence of amplified products indicates the nucleic acid sample contains the nucleotide analyte (Column 8, lines 36-41 and 9B) but Vary et al. and Lane et al. do not teach the nucleotide is enzymatically labeled. However, enzymatic labels were well known and routinely practiced in the art at the time the claimed invention was made as taught by Mullan who teach a method of detecting a polymorphism comprising labeling amplified DNA (Column 10, lines 20-39) wherein the nucleotide is enzymatically labeled (Column 8, lines 33-39). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the label of Vary et al. and Lane et al. with routinely practiced enzymatic labeling based on available reagents and equipment for the

obvious benefit of economy of reagents and equipment and for the known benefits of eliminating the radioactive label.

7. Claims 15 & 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vary et al. (U.S. Patent No. 4,851,331, filed 16 May 1986) in view of Lane et al. (U.S. Patent No. 6,165,714, files 16 December 1997) and Lockhart et al (U.S. Patent No. 5,556,752).

Regarding Claim 15, Vary et al. teach a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample, the method comprising: amplifying a region of DNA comprising the polymorphic locus; labeling the amplified DNA to form labeled amplified DNA products; and hybridizing the labeled DNA products to the probe on a solid support (Column 7, lines 43-49 and Fig. 3 A and B) and optionally detecting the labeled DNA products hybridized to the probe on the solid support (Column 4, lines 44-56) to thereby detect a nucleic acid containing a polymorphic locus (Column 4, lines 53-56) but they do not teach the solid support is a microtiter dish. Lane et al. teach a similar method to determine a nucleotide analyte comprising: amplifying a region of DNA comprising using a primer pair, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe; hybridizing the amplified products to the probe on the support such that the second strand hybridizes to the support; and detecting the amplified products wherein the presence of amplified products indicates the nucleic acid sample contains the nucleotide analyte (Column 8, lines 36-41 and 9B) but Vary et al. and Lane et al. do not teach the solid support is a microtiter dish. However, microtiter dish solid supports were well known and routinely practiced in the art at the time the claimed invention was made as taught by Lockhart et al. who teach a nucleotide detection method wherein probes are immobilized on

a solid support wherein the support is beads (Column 7, lines 27-33) and microtiter dishes (i.e. a polystyrene support having depressed regions) (Column 8, lines 41-44 and 50). It would have It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the solid support of Vary et al. with the microtiter support of Lockhart et al. for the expected benefit simplifying polymorphism identification by immobilizing probes in regionally defined and separate areas to thereby identify polymorphism based on the region of hybridization.

**Conclusion**

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
September 7, 2001

W. Gary Jones
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9/10/01